

STUDIES ON THE CONDITIONS OF ACTIVITY
IN ENDOCRINE GLANDS

II. THE SECRETORY INNERVATION OF THE THYROID GLAND

BY

W. B. CANNON AND MCKEEN CATTELL

From the Laboratory of Physiology in the Harvard Medical School

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II. THE SECRETORY INNERVATION OF THE THYROID GLAND

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"One of the most difficult and yet one of the most important problems of modern physiology is the question of the innervation of the glands of internal secretion." With this sentence Osokin begins a recent paper on the thyroid gland. Among our chief objects in undertaking this series of studies on the electrical phenomena of glands was to throw as much light as possible into the obscure regions of our acquaintance with the innervation of the ductless glands. Because of an interest which one of us had in another research on the thyroid we selected this gland for our first examination.

Histological evidence. That the thyroid is well supplied with nerves has been known for many decades, as a result of histological studies. There has been general agreement among investigators that these nerves have not been distributed solely to blood vessels, but come into relation besides with the peculiar glandular cells of the organ. As far back as 1867, Parameschko (1) found nerves leaving the vessels and passing away as varicose branches in the connective tissue between the follicles. In 1875 Poincaré (2) made similar observations, and intimated that these fibres might have a secretory function. And since then plexuses of nerve fibres about the follicles and connected with the bases of cells have been reported by Crisafulli (3), by Andersson (4), and by Berkeley (5). Andersson's description has recently been confirmed by Rhinehart (6). According to this latest work all nerves entering the thyroid gland are non-medullated; they arise from neighboring cervical sympathetic ganglia, accompany the arteries, and follow their branches after entering the gland. From the perivascular plexuses fibres are given off to interfollicular connective tissue and form there other plexuses completely surrounding the follicles. From

each perifollicular plexus the finest fibrils reach out and end in knob-like enlargements on the basal end of the gland cells.

From the analogy of other glands provided with secretory nerves, we should expect that the cells of the thyroid would be supplied solely by fibres from the autonomic nervous system. The histological evidence, just cited, that only non-medullated fibres enter the gland, gives confirmation to that surmise. These fibres, however, might be derived from both the sympathetic and the cranial divisions of the autonomic system, or from either division alone. It is a matter of considerable significance for understanding the relation of the thyroid to the bodily economy to learn their origin.

Anatomical evidence. After careful anatomical and embryological dissections Briau (7) reported that the thyroid nerves arise from the cervical sympathetic trunk, leaving that trunk at different levels, but originating especially (in man) from the middle cervical ganglion. This mass of nerve cells usually lies upon, or close to, the inferior thyroid artery, hence the name "thyroid ganglion" assigned to it by Haller. It corresponds to the inferior cervical ganglion of the dog and cat. Even what in man has been described as the inferior cervical ganglion is frequently found fused with the first thoracic. It is this fusion of several ganglionic masses at the top of the thorax that makes the stellate.

In man the fibres passing out from the middle (inferior) cervical ganglion form plexuses around the thyroid arteries, Briau states, but chiefly around the inferior artery. According to Poirier and Charpy (8) and other anatomists, branches from the superior cervical ganglion make the superior thyroid plexus about the artery of that name, and penetrate the gland along with it. Henle's observation that the superior laryngeal nerve, and Lindemann's observation that the recurrent laryngeal each sends two or three filaments to the gland, were confirmed by Briau in all his dissections.

In the cat the inferior cervical ganglion lies low in the neck, and the superior cervical is situated well above the level of the thyroid cartilage. The inferior thyroid artery along which in man filaments from the inferior ganglion pass to the gland is inconstant in the cat, and even when present is small. The superior thyroid artery is a regular branch of the common carotid. Langley states (9) that occasionally in the cat a small "accessory" ganglion is found on the cervical sympathetic trunk, about the level of the superior thyroid artery, which sends off gray fibres to that artery. In most animals this ganglion is part of the superior cervical.

Evidence from stimulation or severance of nerves. Further indication of the character and relations of these nerves is found in the experimental work done to determine whether or not they have a secretory function. Evidence has been obtained by stimulating the nerves or severing them, and testing the effects on other functions or on the condition of the gland itself.

In the Bern laboratory Asher and his collaborators have used the method of stimulation and examination of other functions. They have followed a suggestion made by Cyon (10) that the superior and recurrent laryngeals are the secretory nerves for the thyroid. When these nerves were excited Asher and Flack (11) found that the depressor causes a greater fall of arterial pressure and that adrenin raises arterial pressure to a greater height than before. Because the same phenomena occur after intravenous injection of thyroid extract they concluded that the laryngeal impulses call forth a true secretion. Asher and v. Rodt (12) reported that stimulation of the laryngeals increases the efficacy of splanchnic impulses. And Osokin (13) observed that such stimulation magnifies the influence of the vagus on the heart. Although Biedl and Brun (14) were able to demonstrate that the depressor causes a greater fall of pressure after the laryngeal nerves have been excited than before, they were unwilling to concede that this result was a reliable indicator of thyroid secretion, because in the same experiment uniform stimuli applied to the depressor resulted in a variable fall. And Schäfer has testified (15) that he has been unable to confirm, either in the rabbit, the dog, or the cat, the claim that injection of thyroid extract increases the efficacy of the cardiac vagus or the depressor. In any case, whether Asher's criterion of thyroid discharge is trustworthy or not, the method leaves undecided the interesting question whether the impulses are delivered by cranial autonomic or sympathetic neurones. For although the laryngei are branches of the vagus and therefore contain, presumably, elements of the cranial division, they might, on the other hand, serve merely as conveyors of sympathetic fibres.

Somewhat more direct evidence as to the cranial or thoracic origin of the thyroid nerves is found in tests of the iodine content of the gland with and without stimulation. Examinations by Wiener (16), by Rahe, Rogers, Fawcett and Beebe (17), and by Watts (18) agree in showing that the iodine content per gram of gland substance, though varying in different animals, is practically identical in the two lobes of any single animal. Rahe and her collaborators discovered that stimu-

lation of the superior thyroid vessels with the accompanying nerves, or the vago-sympathetic trunk (in the dog), may make the iodine content of the disturbed lobe less than that on the other side by as much as 0.3588 mgm. per gram of gland substance. They concluded, therefore, that a discharge of the peculiar substance of the thyroid takes place in response to nervous stimulation. This conclusion has been supported by Watts (19) who, after stimulating the cervical sympathetic trunk, or the nerve filaments accompanying the superior thyroid artery (in the dog), found a considerable reduction of the iodine content of the thyroid on the stimulated side. After stimulation of the entire sympathetic trunk the average reduction (0.04572 per cent for dry tissue) was more than it was when the thyroid filaments alone were excited (0.03526 per cent).

Additional evidence indicative of sympathetic influence over thyroid activity was obtained by Missiroli and by Wiener. Missiroli (20) found at various periods after section of the sympathetic trunk in the neck characteristic changes in the granules of the secreting cells of the thyroid. Wiener (21) studied the effects of cutting not only the sympathetic, but also other nerves. He severed the vagus on one side (in the dog) above the ganglion nodosum, but without effect—the glands on the two sides corresponded in weight and in iodine content just as in normal animals. The result was quite different after removing the inferior cervical ganglion; within a few weeks a remarkable diminution in size occurred on the operated side (in three cases a lessening of dry weight of 36.9, 48.5, and 11 per cent),¹ and with that a corresponding reduction of the thyroglobulin content. Katzenstein's earlier observation (22) that severance of the superior laryngeal nerve results in a degeneration of cells in the gland, Wiener explains as a consequence of section of sympathetic fibres in the superior laryngeal, because cutting the main trunk of the vagus is without effect.

He concluded that if paralysis of the sympathetic causes atrophy and a lessened iodine content, stimulation must cause hypertrophy and increase of thyroglobulin—a conclusion which is opposed, however, by the results of the stimulation experiments already described.

The various interpretations which have been given to the experiments above sketched will be left to later discussion. For the present it is sufficient to state, in summary, that the evidences from histologi-

¹ In a cat with the thoracic sympathetic cord cut just below the stellate ganglion we found after four months the thyroid lobe on that side weighing 0.167 gram, that on the other side 0.256 gram.

cal and anatomical examination, and from experimental excitation and severance of nerves, point towards a definite influence of sympathetic impulses over thyroid activity.

*Electrical evidence for the innervation of the thyroid gland.*² In a previous paper (23) we have given reasons for believing that the action current of a gland is a reliable indication of secretory activity. The two phenomena, as tested in a gland with external secretion, appear together, vary together in duration, disappear together, and are independent of accompanying vascular disturbances. This close concomitance of secretion and electrical change justifies the use of the electromotive phenomena of a gland to determine the conditions of its activity.

Methods. The general methods which we have employed in this research we have described in the first paper of this series. We found in studying the thyroid gland that urethane (2 grams per kilo) was unsatisfactory as an anaesthetic, and also that deep etherization was capable of abolishing effects that appeared readily when the anaesthesia was not so profound. In some experiments we obtained consistent results on dispensing with any anaesthetic after pithing the brain and the cord to the mid thorax. Since the blood flow was thus much diminished, however, we decided that etherization to the point of immobilizing the animal was a less upsetting procedure, and consequently we have employed that method in most of our work. In a few cases we have used curare after decerebration.

Through an opening between the second and third ribs the right sympathetic trunk was laid bare. Shielded electrodes which could be fixed in place³ were slipped under the nerves just below the stellate ganglion, and the conductivity of the fibres below the electrodes was destroyed by crushing. The skin was now drawn close around the

² The brief description of experiments which follows gives no indication of the troubles which were encountered in the course of our investigations. The method was new to us, it was new in its application to glands of internal secretion, and was beset not only with experimental difficulties, but also with dangers of serious error. We lost much time before we learned that deep anaesthesia would check secretion. We had difficulties in securing immobility and excluding the effects of action in neighboring tissues. We also had troubles with electrodes and with diffuse action of chemical stimuli. All these and other conditions we were compelled to examine for their influence on the processes being studied and on the methods which we were using. After we had learned the pitfalls, however, and could intelligently avoid them, we found it possible to demonstrate in one preparation practically all the points here described.

³ See Cannon and Nice: This journal, 1913, xxxii, p. 47. A small spear-shaped steel hook reaching out of the wood held the rod in any position desired.

projecting part of the electrodes. Artificial respiration was maintained by an interrupted air current. The leading off (gelatin) electrodes, connected with the galvanometer, were set, one in contact with the right thyroid gland which had been exposed with as little manipulation as possible, the other on the connective tissue inside of a little flap of skin turned back from the neck at about the thyroid level, or at times on the trachea. Movement of the parts near these electrodes, due to respiration, was practically abolished by clamping the tracheal cannula and pulling it slightly towards the chest. Usually just after the gland was exposed and the gelatin electrodes were applied a period of repeated adjustment had to be passed through before the tissues and the compensating current were in equilibrium.

Effects of sympathetic stimulation. Numerous observations have shown that when the sympathetic trunk immediately below the stellate ganglion is stimulated by a weak tetanizing current a definite difference of potential is developed between the two leading-off electrodes. This phenomenon does not occur if the stimulus is applied to other nerves in the upper thorax, e.g., the central end of the cut phrenic. It is not, therefore, due to any spreading of direct physical influences from the thorax to the upper neck region. Furthermore it does not occur if the leading-off electrode on the gland is transferred to a neighboring muscle, and the thoracic trunk is then stimulated. It is, therefore, due to some change in the thyroid itself. That the electrical change has a characteristic and long latent period—usually between 5 and 7 seconds after the stimulus is started—which is considerably longer than that for the submaxillary gland, confirms the other evidence that the change is not direct physical effect, but a peculiar and distinguishing manifestation of thyroid activity.

In the first paper of this series, on the submaxillary gland, records were published illustrating the gland negative to the skin (through external connections) as a result of nerve stimulation, and also, but under different circumstances, the gland positive to the skin as a result of the same stimulation. The reversal of skin currents, also, in consequence of repeated nervous excitations during a short period, was referred to. Reversal of the current is not yet explained, but that it does not invalidate the electrical phenomenon as a criterion of activity is proved by the observation that a typically increased flow of saliva follows chorda stimulation, whether the gland becomes negative or positive to the skin (24). These facts are recited here because, in our experience, the thyroid gland, although usually negative to the skin

after stimulation, is sometimes positive for a moment and then negative. More rarely a purely positive relation to the skin is present.

Illustrations of these three types of responses are given in figure 1, *A* and *B*, and in figure 2. Other records taken before and after these in the same animals had the same peculiarities. The latent period in the case of figure 1 *B* was longer than in the case of *A*, a condition which was noted in several other instances in which the reaction occurred in

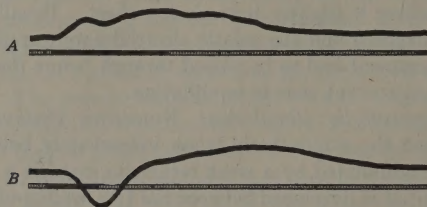


Fig. 1. Action current of the thyroid gland on stimulating thoracic sympathetic cord. Here and in other records time is registered in half-minutes. *A*, stimulation one minute; gland negative to subcutaneous fascia. *B*, stimulation a half-minute; gland first positive, then negative.

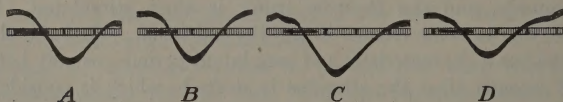


Fig. 2. *A*, 2.39. Thyroid action current from stimulating for a half-minute the thoracic strand, with all nerves intact. Gland positive to trachea. *B*, 2.43. The same, except recurrent laryngeal nerve cut (2.41). *C*, 3.09. The same, except, in addition, superior laryngeal nerve cut (2.48). *D*, 3.21. The same, except, in addition, cervical sympathetic cut above inferior cervical ganglion (3.21).

two phases. The greater delay under these circumstances may be due to an initial balance between two opposed processes; one of these processes may then hold primary predominance, only later to give way to the other.

The course of the sympathetic fibres. The action current evoked by stimulating the sympathetic nerve in the chest persists although the recurrent laryngeal nerve is severed. Figure 2 *A* presents the record of electrical change in the thyroid gland when the sympathetic strand

was stimulated (at 2.39) with all the cervical nerves intact; and figure 2 *B*, a record from the same animal (at 2.43) after the recurrent laryngeal was cut. The conditions of stimulation were the same in both instances. The response was that of a positive relation of the gland to the indifferent tracheal cartilage. The operation has evidently not affected the influence of impulses started in the sympathetic fibres of the chest.

The action current of the thyroid persists also after the influence of the superior laryngeal nerve has been abolished. In figure 2 *C* the action current of the thyroid is registered on stimulation of the sympathetic trunk in the thorax (at 3.09) after severance of the superior in addition to the recurrent laryngeal. The stimulus was applied for a half-minute just as before; the larger response is probably not significant of a favorable effect of the operation, because, as proved by other instances in which the same experiment was performed, the response after the nerve cutting may be slightly less than before.

A further step in determining the path of the impulses which cause the electrical change is taken when the cervical sympathetic fibres are sectioned, and the thoracic trunk is stimulated. Figure 2 *D* is a photograph of the electrical change of the thyroid in the same case from which the other records in figure 2 (*A*, *B* and *C*) were taken, but after the cervical sympathetic trunk in addition to the laryngeal nerves had been cut across. Obviously these operations have not interfered with the reaction of the gland. Although the reaction continues after the sympathetic fibres have been transected in the neck, excitation of these fibres central to the cut produces the characteristic effect.

The question now arises as to where the relay between preganglionic and postganglionic fibres is situated. As already seen, two ganglionic masses are present in the course of the cat's cervical sympathetic—the inferior and the superior, with occasionally an “accessory” mass near the superior thyroid artery. That all the fibres leading to the gland do not originate in the superior ganglion or ganglia is proved by figure 2 *D*, for in that instance the sympathetic trunk had been cut across between the two cervical ganglia. It can be assumed therefore that in the cat a relay of some of the fibres occurs in the inferior ganglion.

Evidence for a relay in the superior region was obtained by the nicotine method of blocking impulses at sympathetic synapses and also by serial sectioning of the nerve from above downwards. In one of the experiments in which nicotine was used stimulation of the cervical sympathetic sent the galvanometer from +2 to -3, and thence out

to +94. A pledget of cotton wet with 1 per cent nicotine was now laid in contact with the superior cervical ganglion. Eighteen minutes later the nictitating membrane was not withdrawn when the sympathetic trunk was stimulated, but the galvanometer was sent out to +76; eight minutes later another stimulation for a half-minute sent it to +78. Now a slender strand of cotton wet with the nicotine solution was laid along the sympathetic trunk from the superior cervical ganglion to a point 2 cm., below the thyroid cartilage. After 20 minutes, stimulation of the cervical trunk had no effect. That this was not due to any deleterious effect of nicotine in the gland was proved by exciting the gland to activity by chemical stimulation (in a manner to be described later), and also by applying the electrodes to fibres on the superior thyroid artery and finding that repeated stimulation sent the galvanometer in the plus direction. In another experiment in which the sympathetic was serially cut, first across the upper pole of the superior cervical ganglion, second across the middle, and then crushed directly below the ganglion, stimulation of the cervical sympathetic trunk still persisted in causing marked action currents in the thyroid gland. The sympathetic trunk was now severed about 1 cm. below the ganglion, and thereupon the electrical effect of stimulation disappeared. These experiments indicate that in these animals the upper relay region was not situated in the superior cervical ganglion itself, for when impulses to the eye had been blocked in that ganglion by nicotine or the fibres had been cut below it, the electrical change in the thyroid still followed excitation of the sympathetic. The impulses were shut off, however, when the nerve was cut some distance below the ganglion or when nicotine was allowed to act on that region, i.e., the region in which Langley found the "accessory" ganglionic cells with a distribution of fibres to the thyroid. In another instance, after nicotine, applied to the superior cervical ganglion, had failed to prevent the thyroid action current (although effectively blocking nervous influence on the eye), a strong carbolic acid solution touched on the superior thyroid artery, in order to destroy nervous conductivity, quickly abolished the phenomenon.

After the cervical sympathetic trunk has been cut above the inferior cervical ganglion and a record of the thyroid action current has been obtained by stimulating the thoracic sympathetic cord (as in figure 2, D), excision of the inferior cervical ganglion abolishes the effects of stimulation.

From the foregoing evidence we may conclude that both in the superior and in the inferior ganglionic masses of the cervical sympathetic,

impulses to the thyroid gland pass from preganglionic fibres to the out-lying neurones.

The question of vagus control. The prominence of laryngeal stimulation in previous experiments, especially the experiments carried on in the Bern Laboratory, raises the question as to whether the thyroid gland like the submaxillary of the cat, is subject to control by cranial as well as by sympathetic autonomic fibres. To secure evidence on this question, we had to stimulate the vagus trunk before its union with the cervical sympathetic strand. And since the vagus contains motor fibres to muscles of the larynx, which might through their contractions affect the galvanometer, it was necessary to use a curarized preparation. We decerebrated, and then, in order to avoid as far as possible the danger of disturbing the gland cells, injected intravenously barely enough curare to abolish reflexes. We bared the vagus at its point of emergence from the skull, tied a thread about it there, cut proximal to the thread and applied the stimulus to the nerve as close as possible to the thread, i.e., as far as possible from the union of the vagus and sympathetic at the superior cervical ganglion. We have not succeeded in obtaining any evidence of any influence of

vagus impulses on the thyroid gland. We have stimulated the nerve with the gland at rest, and with the action current developing as a result of sympathetic impulses, and with the action current disappearing—but no change was produced. Figure 3 *A* is a record of the action current of the right thyroid as a result of stimulating for a half-minute the right thoracic sympathetic cord (at *a*). After a latent period of about 25 seconds (longer than with ether—probably due to curare and a lowered body temperature), the galvanometer began to indicate the gland negative to the indifferent tissue. When the galvanometer had moved to +12, the right vagus trunk was stimulated for a half-minute with the same stimulus (at *b*). The movement continued without check to +45, and was followed by a slow return. That vagus stimulation had no noteworthy influence, is shown by comparing figure 3 *A* with figure 3 *B*, a record taken three minutes after figure 3 *A*, and registering the

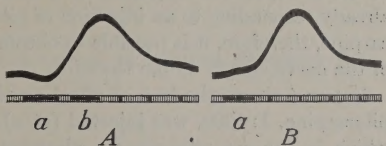


Fig. 3. *A*, 4.27. Thyroid action current on stimulating for a half-minute the thoracic cord at *a*, and the main vagus trunk at *b*. *B*, 4.31. The same, on stimulating the thoracic cord alone at *a*.

action current when the thoracic cord alone was excited for a half-minute (at *a*). The close resemblance of the two records proves that the vagus has been neither an exciter nor an inhibitor of thyroid activity.

From this evidence we may conclude that the laryngeal branches of the vagus nerve are not secretory nerves of the thyroid gland. And the fact that action currents of undiminished amplitude follow sympathetic stimulation after these nerves are severed (see figure 2) indicates that they are not highly important vehicles for sympathetic fibres.

Pharmacological evidence. A way of securing further evidence bearing on the source of impulses affecting the thyroid is found in the use of drugs having specific effects on cranial autonomic nerve endings. It is well known that pilocarpine stimulates viscera innervated by cranial autonomic nerves and affects these organs in such manner as to mimic the action of nerve impulses. In the case of the submaxillary gland, for instance, chorda impulses are commonly ineffective if the gland is already responding to an injection of pilocarpine (25). By use of pilocarpine, therefore, it is possible to obtain deeper insight into the nature of the nerve supply to the thyroid.

Figure 4 shows the lack of effect on the thyroid gland when 1 cc. of pilocarpine, 1:1000, was injected (at *a*) intravenously. This is a dose which in the cat produces an abundant and long-continued salivary secretion, accompanied, as shown in the first paper of this series, by a persistent electrical change. But in the thyroid gland pilocarpine does not induce an action current—under no circumstances have we observed consistent indications of an effect on the thyroid which could be ascribed to this drug. These results are in accord with the failure of vagus impulses to influence thyroid activity; they support the conclusions from the histological studies by Schmid (26) and by Osokin (27), and the chemical studies by Wiener (28) that pilocarpine is wholly without effect on the thyroid; and they are further evidence against the opinions of Wyss (29) and of Andersson (30), based on microscopic appearances, that pilocarpine produces changes in the thyroid similar to those seen in a secreting gland. The weight of evidence, therefore, is opposed to a cranial autonomic supply to the thyroid gland.

The influence of anemia on thyroid activity. In a recent paper Watts (31) has reported that diminishing by mechanical means the blood supply to one thyroid lobe, periodically (for 2 seconds every 10) during approximately three hours, lessens the iodine content of that lobe relative to the other. The discrepancy between the two lobes was not so great as when a stimulus was applied to the cervical sympathetic or

to the fibres on the superior thyroid artery, but such stimulation, it was pointed out, would cause a greater check to the blood flow than could be caused by mechanical compression of the arteries. Watts and Carlson conclude, therefore, that shutting down of the blood supply by vascular constriction accounts for all changes in the thyroid thus far shown to be caused by stimulation of nerves.

We have put to test the idea that anemia accounts for thyroid secretion. In figures 1 B, 2 and 3 the period of stimulation was only a half-minute. Even if the result were a total stoppage of the flow through the gland, it would not persist after stimulation ceased. That complete anemia of the thyroid for a half-minute is practically without effect is shown in figure 5. For two periods, at *a* and at *b*, the blood

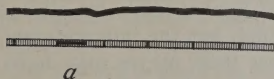


Fig. 4. Absence of thyroid action current on injecting pilocarpine (1 cc., 1:1000) at *a*.

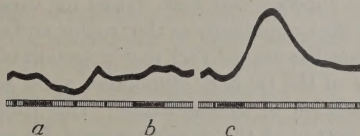


Fig. 5. Galvanometric changes in the same animal when thyroid completely anemic at *a* and at *b* (a half-minute each) and when stimulated (thoracic cord) a half-minute, at *c*.

supply to the gland was entirely excluded. This was done by first tying the left carotid artery low in the neck, and then, at *a* and at *b*, occluding the right carotid. It was impossible to avoid a slight amount of disturbance from manipulation, which would account for the uneven line of record. The effect of this procedure is to be compared with the effect of stimulating for a half-minute the thoracic sympathetic cord in the same animal, at *c*. Obviously nerve stimulation has an influence on the thyroid very different from anemia.

Discussion of the evidence for thyroid innervation. The observations presented in the foregoing pages are concerned mainly with three questions: (1) the nature of the innervation of the thyroid gland, (2) the

mode of action of the nerve impulses whether directly secretory or not, and (3) the character of the process underlying the electrical change.

We believe that the evidence is now convincing that the nerves of the thyroid are exclusively derived from the sympathetic division of the autonomic system. The histologists find non-medullated fibres reaching to the base of the follicular cells; the anatomists distinguish only cervical sympathetic nerves entering the gland; sympathetic section causes marked atrophy of the gland structure whereas vagus section has no influence; sympathetic stimulation gives rise to a striking action current, whereas excitation of the main vagus trunk, and exhibition of pilocarpine as a cranial autonomic stimulant are without effect. All these facts are harmonious in bearing testimony to an exclusive sympathetic control of thyroid activity. The observations on the effects of exciting the laryngeal nerves, made by other investigators, are not thereby rendered invalid, but the interpretation placed upon them is that whatever influence these nerves may have on thyroid function is exerted by way of sympathetic fibres contained in them—a possibility which, as we have seen (p. 59), has anatomical justification.

The question as to whether the nerves supplied to the thyroid are truly secretory in function has been raised for various reasons. Although regarding the sympathetic as the trophic and secretory nerve of the thyroid, Wiener has argued (32) that if section of the sympathetic produces atrophy of the thyroid, stimulation must produce hypertrophy, and accumulation of thyroglobulin. This conclusion, however, is not justified. Section of the chorda tympani, for example, results in a gradual lessening of the size of the submaxillary gland (33), and yet the normal function of the nerve is to cause a secretory discharge. Also Wiener's argument is opposed by the discovery that stimulation of the cervical sympathetic trunk actually lessens the iodine content of the gland. The view of Watts and Carlson that sympathetic impulses lessen the iodine content by producing anemia fails to regard both the direct nerve supply to the gland cells and also the reasonable assumption that these fibres have a function apart from the fibres distributed to blood vessels; and furthermore their view is opposed by the evidence presented in this paper that although sympathetic stimulation induces a marked action current in the thyroid, total anemia for an equivalent period brings forth no noteworthy electrical change whatever. Prolonged anemia may indeed lessen the iodine content of the thyroid, but tissues respond to a variety of stimuli; and merely because, for example, uremia causes convulsions, it is not proper to attribute all

convulsions to uremia. The conclusions of Watts and Carlson, therefore, seems to us defective in failing to regard important conditions which affect response. Still another doubt regarding secretory fibres has recently been raised by Manley and Marine (34) who found that when thyroid tissue is transplanted to various parts of the body it grows where placed, and functions and reacts as a normal gland would do. There is no logical opposition to secretory nerves in these experiments. The adrenal glands, for example, will serve the routine needs of the body when their secretory nerves are cut, for the animal lives with the nerves transected, but he promptly dies if the adrenals are removed. The capacity of an organ to give service, as the heart may do, though separated from the central nervous system, should not lead to the conclusion that its nerves are without influence. This doubt of the existence of specific secretory nerves to the thyroid has not, therefore, any convincing significance. And like the other suspicions as to the reality of these nerves, this one is based, as we see it, on a failure to consider all the evidence.

A part of the evidence for secretory nerves is, to be sure, first presented in this paper. But it is based on the assumption that the action current is a sign of secretory activity—and *that* might be doubted. To some degree the assumption is based on analogy with the sub-maxillary gland. An action current in that gland is the regular concomitant of secretion, and fails when secretion fails. The action current of the thyroid has a latent period characteristic of physiological processes, it may outlast the period of stimulation by many minutes, it appears after stimulation of sympathetic fibres—the filaments of which are known to be distributed to the gland cells—and all these evidences indicate that the action current is a true signal of physiological events taking place in the gland as a result of nerve stimulation. The concordant testimony of different investigators that precisely the sort of stimulation which provokes this process, will, if continued, result in a measurable diminution of the iodine content of the disturbed lobe affords clear proof that the process signalled by the galvanometer is one of secretory discharge.

SUMMARY

Histologists describe non-medullated nerve fibrils reaching to the cells of the thyroid gland. Anatomists find that fibres going to the thyroid gland arise in cervical sympathetic ganglia.

Previous investigators have shown that severance of its cervical sympathetic nerves causes atrophy of the thyroid, and that stimulation of these nerves causes a diminished iodine content of the gland. Severance of the vagus supply has no effect.

If the thyroid gland and neighboring indifferent tissue are connected through a galvanometer, stimulation of the sympathetic cord high in the thorax evokes an action current after a latent period varying usually between five and seven seconds. This effect persists after the superior and the recurrent laryngeal nerves are severed. Evidence is presented that the impulses pass to outlying neurones whose cell bodies are located close below the superior cervical ganglion and also in the inferior cervical region.

Stimulation of the main trunk of the vagus in a curarized animal, and injection of pilocarpine (as an exciter of cranial autonomic endings) have no effects on the thyroid gland.

Anemia made total by clamping the carotids for a period equal to that of sympathetic stimulation produces no noteworthy electrical changes in the gland.

The conclusion is drawn therefore that the non-medullated nerves distributed to thyroid cells belong to the sympathetic and not to the cranial division of the autonomic system, that their effects are not indirect through alterations of blood supply, that they are indeed true secretory nerves.

The arguments against this conclusion are discussed.

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